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Gas chromatography–mass spectrometry determination of the migration of phthalate plasticisers from polyvinyl chloride toys and childcare articles

A.O. Earls*, I.P. Axford, J.H. Braybrook
Consumer Safety and Tobacco Products, Room 3/8, LGC Ltd., Queens Road, Teddington, Middlesex TW11 OLY, UK

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Abstract

Two laboratory-based linear horizontal agitation methods for determining a range of phthalate esters from soft polyvinyl chloride (PVC) toys are presented in compliance with EU legislation. Both of these methods were validated through interlaboratory trials using a PVC reference disc and four soft PVC toy/childcare articles intended or likely to be mouthed. Two of these commercial samples contained diisononyl phthalate (DINP), one diisodecyl phthalate (DIDP) and one bis(2-ethylhexyl) phthalate (DEHP). Acceptable repeatability (*r*, within-laboratory) and reproducibility (*R*, between-laboratory) data were demonstrated for both the analytical detection technique (GC–MS) ($r=9.8\%$ and $R=8.1\%$) and agitation/extraction procedure ($r=21.9\%$ and $R=35.3\%$ at 37 °C; $r=22.7\%$ and $R=31.1\%$ at 65 °C) for DINP. This was achieved through the participation of six laboratories. The remaining three phthalates from the EU Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) list—dibutyl phthalate (DBP), benzyl butyl phthalate (BBP) and di-*n*-octyl phthalate (DnOP)—were not tested due to the unavailability of suitable materials.

Keywords: Agitation methods; Migration; Toys; Phthalates; Poly(vinyl chloride)

Phthalic acid esters (''phthalates'') are the most commonly used plasticizers in polyvinyl chloride (PVC) based products due to their compatibility and softening capability [1]. The plasticiser content can be up to 50% by weight. Although named as diesters of phthalic acid (benzene 1,2-dicarboxylic acid), they are produced by the esterification of phthalic anhydride with long-chained alcohols (C7–C10). They have widespread use in consumer products such as children's toys, childcare articles, and household and industrial hardware including electrical cabling, PVC flooring and water pipes. Additional sources of these chemicals are PVC Infusion Lines, exposing infants to large amounts of plasticizer [2].

Several techniques have been described for the determination of phthalates. Reversed-phase high-performance liquid chromatography (HPLC), for instance, is used for the determination of DBP, DEHP and DIDP in industrial emissions [3]. BBP, DEHP and DIDP were analysed in total diet samples, baby food and infant formulae by gas chromatog-

*Corresponding author. Fax: +44-20-8943-1050.
E-mail address: andy.earls@lgc.co.uk (A.O. Earls).

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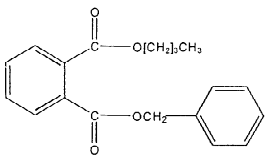
raphy–mass spectrometry (GC–MS) operated in selected ion monitoring (SIM). Identification was based on comparison of retention time and ion ratios for each of the target analytes [4]. Additional procedures have been described for the qualitative identification of plasticizers in medical products by GC–MS, and for total phthalate content in toy materials by GC–FID (flame ionisation detector) [5,6]. Limited methods are available on the migration of these substances from PVC toys into artificial simulants, however one method describes the migration of DINP and DEHP in saliva simulant using the ''Head over Heels'' agitation method with HPLC [7].

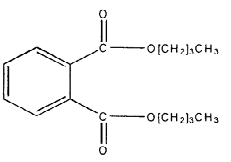
The phthalates (see Table 1 for structures and abbreviations) have been found to migrate from PVC-based toys and childcare articles, especially those which are known to be mouthed—DEHP and DINP being the most common. Based on opinions, the CSTEE has established migration limits for each of these phthalates from available toxicological data; up-to-date information should be sought when addressing this issue. The CSTEE working group assessed the health risk to children exposed to phthalates in toys. An exposure dose was calculated from the maximum amounts which migrated when a surrogate for a phthalate containing PVC-toy of 10 cm^2 is extracted for 3 h by a model saliva solution under dynamic conditions. Risk assessments were based on a body weight of an infant of 8 kg. This may be a worse case approach since there is not a standardised or validated extraction method. Critical effects for the phthalates were assessed with a margin of safety. NOAEL (No-Observed-Adverse-Effect-Level) values were identified for four phthalates (DINP, DnOP, DEHP, DIDP) and L(lowest)OAEL for the two remaining phthalates, DBP and BBP. From this information safety margins were incorporated between the NOAEL and exposure data. As a result of these findings, the CSTEE recommended the following guideline values for maximum permissible extracted amounts (for a child of 8 kg body weight); 0.8 mg DBP, 3.0 mg DnOP, 0.3 mg DEHP, 1.2 mg DINP, 2.0 mg DIDP and 1.6 mg BBP per 10 cm^2 of article mouthed over a 3 h time period. Hazards associated with phthalates such as DEHP include reproductive toxicity and teratogenesis, and malformed offspring in mice [8]. A recent publication describes the relationship between testicular cancer and occupational exposure to PVC containing phthalate plasticizers [9]. A review and risk assessment on the potential toxicity effects of DINP, exposure levels of children to DINP migrating from PVC products, and a risk assessment of the potential adverse effects has been documented [10]. A comprehensive evaluation of the health effects of DEHP details human and animal health effects and provides toxicological information after its exposure and relevance to public health [11].

This paper describes two methods for the determination of the migration of phthalates into saliva. They are based on linear horizontal agitation, and have been validated by interlaboratory trial [12]. GC–MS was employed to provide the analytical

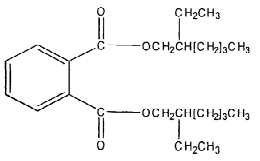
Table 1
Structures of six phthalate components with defined limits for migration from childcare articles and toys set by the CSTEE



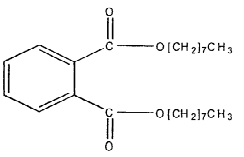
Benzyl butyl phthalate (BBP)



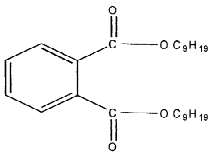
Dibutyl phthalate (DBP)



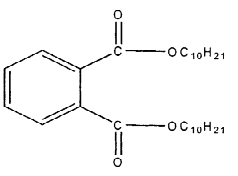
Bis(2-ethylhexyl) phthalate (DEHP)



Di-n-octyl phthalate (DnOP)



Diisononyl phthalate (DINP)



Diisodecyl phthalate (DIDP)

Both DINP and DIDP are mixtures of isomers.

specificity for ensuring conformity of PVC toy and childcare articles with the CSTEE migration limits.

1. Migration test methods

Most analytical test methods are developed to measure the total concentration of a component in a test material. Migration methods, on the other hand, are intended to determine the extent to which a component can be extracted from a test material under conditions relevant to real-life activities, and the results are dependent on conditions of migration. In comparison with total concentration method results, good statistical agreement between migration results is difficult to obtain. Generally, the relative concentrations of a group of substances in a sample are not reflected in their relative recoveries from migration tests, because the spatial distribution and kinetics of release of the component contribute to the result. Two mechanical test methods (''Simulated'' and ''Stringent''), which mimic the way phthalates migrate from PVC-based products, have been developed at the LGC (Laboratory of the Government Chemist). The methods are based on linear horizontal agitation under strictly controlled conditions of temperature, mode of mechanical agitation (pounding), agitation frequency, contact time (including ''continuous'' and ''replenishment'' testing), and volume and content of saliva simulant. The methods are aimed at representing the human oral environment as far as is practicable in the laboratory. One of the main difficulties in developing a laboratory-based (in vitro) phthalate migration method for childcare articles has been the lack of validated in vivo oral migration data from children. The Dutch Consensus Group (DCG) has provided data derived from child observation and in vivo adult ''chew and spit'' studies [13]; a standard PVC disc and two forms of a ''commercial'' soft PVC sample were used. Additional data on in vivo adult ''chew and spit'' studies on ''standard PVC sheet'' and ''commercial'' soft PVC samples has been provided by Steiner et al. [14].

Both the ''Simulated'' and ''Stringent'' methods have been designed to correspond closely with the mean oral contact time of young children with toys, and with mean adult in vivo migration levels of phthalates from PVC toys. A 10 cm^2 total surface area was selected to correspond to the surface area of a child's open mouth, as this gives the typical surface area available for mouthing at any one time. The difference between these methods is temperature and mode of agitation. To establish conditions for the Stringent method, which aims to achieve the target migration value of 9 $\mu g/10\ cm^2/min$ for DINP, the PVC reference disc was analysed at four alternative temperatures (37, 50, 60 and 70 °C), increasing temperature clearly indicating a near exponential increase in plasticiser migration (Fig. 1). The target value was achieved between 60 and 70 °C. The target migration value was set by CSTEE on the basis of the DCG human volunteer study. In contrast, the Simulated method aims to reflect physiological conditions more closely. Because of the safety hazards and impracticalities of using human saliva in a laboratory-method, a saliva simulant was preferred. In this study, a Dutch saliva simulant was adopted for the determination of phthalate migration. A 100 ml/h (10 ml/cm^2 per h) volume was selected, mimicking the mean rate of saliva production stimulated by active mouthing of an object by adults (1.5 ml/min). Two methods of ''contact'' were studied—namely, continuous testing and replenishment. Continuous testing involves contact of test sample with a single portion of saliva over a fixed interval. Replenishment is the removal of saliva in contact with the test material and replacement with a fresh portion; this may occur once or more over the interval determined for the whole test. Replenishment is

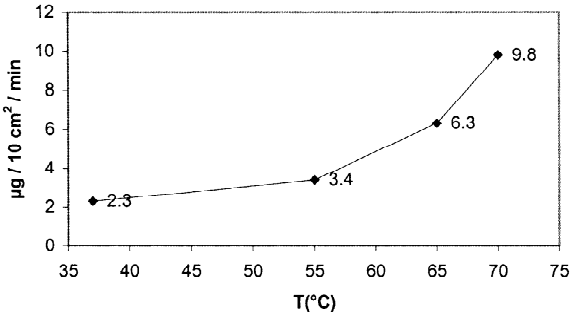


Fig. 1. Effect of temperature on mean migration level of DINP. The PVC reference disc was analysed by the stringent method at four alternative temperatures.

more representative of the realistic use of toy and childcare articles.

2. Methodology

Because of the ubiquity of plasticizers, and the tendency of residues to persist, all glassware is washed before and after use, acid rinsed with 5% nitric acid, rinsed with distilled water and further rinsed with acetone–methanol (1:1, v/v), then dried. Samples need to be stored so that they are not in contact with plasticised surfaces. New batches of chemicals, reagents and distilled water were screened before use in analytical determinations, for instance by evaporation and concentration of organic solvents to measure background levels of phthalates by GC–MS.

3. Test samples and sampling

A PVC-based reference sheet of known composition (38.5% DINP) and origin was used to validate both migration methods. Samples measuring approximately 10 cm^2 (total surface area) was accurately measured with a ''metal punch'' and rinsed in deionised water. Toys were selected and purchased from retail outlets as additional standard items, representing different phthalates and levels of migration. A blank sample, without the reference disc was analysed with each batch of toy samples to measure background levels within the extraction method.

4. Chemicals and reagents

HPLC grade dichloromethane, *n*-hexane and propan-2-ol were from Fisher Scientific, Loughborough, UK and Sigma–Aldrich, Poole, UK. Components of the saliva simulant were from Fisher Scientific. Phthalate standards of 99% purity, were from Sigma–Aldrich.

5. Saliva simulant solution

The Dutch saliva solution comprised: 0.82 m*M* magnesium chloride (0.08 g/l), 1.0 m*M* calcium chloride (0.11 g/l), 3.3 m*M* di-potassium hydrogen phosphate (0.57 g/l), 3.8 m*M* potassium carbonate (0.52 g/l), 5.6 m*M* sodium chloride (0.33 g/l), and 10 m*M* potassium chloride (0.75 g/l). The potassium and sodium salts were dissolved in distilled water before adding the magnesium and calcium salts and making up to 1 l. The pH of the solution was adjusted to 6.8 by dropwise addition of 3 mol/l hydrochloric acid.

6. Migration methods

The samples were agitated in a Grant SS40-2 linear/horizontal shaking water bath.

6.1. Simulated method

A 10 cm^2 test sample was placed in a 250 ml glass conical flask with 50 ml saliva simulant solution (pre-heated to 37 °C) and 10 glass balls, ensuring complete submersion of the sample. The flask was stoppered and placed in a shaking waterbath at 37 °C for 60 min, with an amplitude of movement (stroke length) of 38 mm and an agitation speed of 200 strokes/min. After 30 min the saliva simulant solution was replenished, and a second 50 ml portion of saliva added. The two portions of saliva were combined, and extracted with three successive 25 ml portions of dichloromethane. The extracts were combined and reduced to about 5 ml in a Kuderna–Danish (KD) evaporator. The final 5 ml of dichloromethane was taken to dryness under nitrogen flow and made to 2 ml in *n*-hexane.

6.2. Stringent method

The Stringent method was performed identically with the simulated method, except that the saliva simulant solution was at a temperature of 65 °C and stainless steel balls were used.

7. GC–MS for the identification and confirmation of phthalates

GC–MS was chosen for determination of phtha-

late plasticizers because it is highly specific and now widely available. For complete confidence, particularly where results exceed regulatory limits or are questionable, the GC–MS should comply with certain criteria: the chromatogram has peaks with the expected retention times and acceptable peak symmetry with minimal tailing. Peaks for interfering ions in excess of 25% of the base peak are absent; the relative responses of the qualifier ions to the quantifying ion are within an acceptable range of 10%. The most abundant ion formed in the mass spectrometer is called the base peak. In the mass spectra of phthalates the base peak is indicated at the m/z value 149, for this determination this is referred to as the target ion for quantification. The relative abundance of other peaks in the spectrum is expressed as percentages of the abundance of the quantifying ion.

7.1. GC–MS conditions

Phthalate analysis was performed on a Hewlett–Packard model 5890 Series II gas chromatograph fitted with a HP5971A mass-selective detector.

Separation was performed with a DB-17HT (50% dimethyl–50% diphenyl polysiloxane) GC column, 30 m, 0.25 mm ID with a film thickness of 0.15 μm. The column was held at 60 °C for 3 min, ramped at 10 °C/min to 290 °C, and finally held for 10 min. The gas chromatograph was operated in split/splitless injection mode at a temperature of 290 °C. The operating temperature of the MSD was 280 °C. A HP 5971 mass selective detector was used in full scan electron ionisation (EI) mode, and data were acquired over the range m/z 50–500.

8. Results and discussion

GC–MS was chosen for the analysis of phthalates in PVC-based childcare articles and toys. Although selected ion monitoring (SIM) provides higher sensitivity, all analyses were performed in full scan mode, allowing additional identification. Identification and quantification of PVC used the extracted ion m/z 149 for each of the phthalates under test. The confirmation of presence was monitored by the following qualifier ions which are summarised in Table 2; m/z 279 (DEHP and DnOP), m/z 223 (DBP), m/z 91 (BBP), m/z 293 (DINP) and m/z 307 (DIDP). Calibration standards of 2, 5, 10, 15 and 20 μg/ml were prepared in *n*-hexane for DEHP, DnOP, DBP and BBP and 50, 100, 200, 400 and 500 μg/ml for DINP and DIDP. These concentrations include both extremes of the concentration range expected in test materials. Because of co-elution of three of these phthalates, two separate mixtures were prepared for these standards, one containing DBP, DEHP, BBP and DINP and the second DnOP and DIDP. From Figs. 2 and 3 it can be noted that two of these phthalates, namely diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP), are mixtures of many isomers, and are detected as correspondingly broad peaks, which take about 2 min to elute.

In order to construct a calibration line, a regression of peak area abundance on concentration was undertaken using the external standard calibration method. The total areas of each analyte were processed from the ion abundance of the quantifying ion followed by confirmation using the qualifier ions

Table 2
GC–MS retention times (t_R), with quantifying and qualifier ions for the six phthalate compounds listed by the CSTEE

Compound	t_R (min)	Quant ion (m/z)	Qualifier 1 $(M-R)^+$	$(M-OR)^+$	% Abundance	Qualifier 2	% Abundance
Dibutyl phthalate	19.18	149	223		3.10	205	2.40
Bis(2-ethylhexyl) phthalate	23.48	149	279		6.20	167	29.90
Benzyl butyl phthalate	23.98	149		206	14.6	91	64.7
Di-n-octyl phthalate	24.49	149	279		7.56	261	2.10
Diisononyl phthalate	24.0–26.5	149	293		13.11	167	2.20
Diisodecyl phthalate	25.0–27.5	149	307		12.12	167	2.32

The qualifier ions were indicated by the NIST mass spectral library software incorporated into the software and may serve as target ions depending on the presence of additional phthalates not present on the CSTEE list. The percentage abundance is the relative intensity to the quantifying ion. The reference standards were prepared in *n*-hexane and injected directly onto GC–MS.

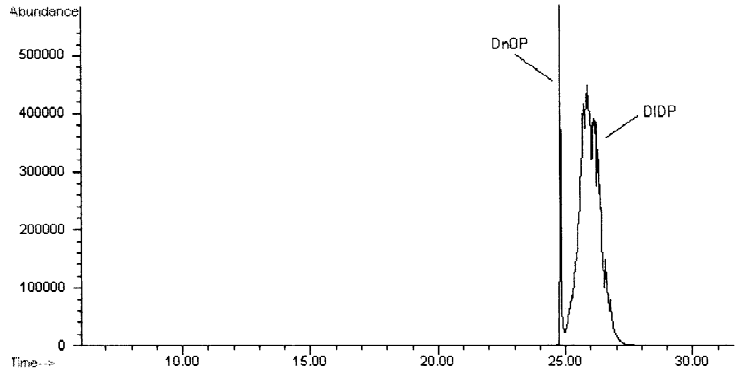


Fig. 2. Total ion chromatogram of di-*n*-octyl phthalate and diisodecyl phthalate in full scan mode. Temperature programme and MS parameters are in GC–MS conditions.

summarised in Table 2. Replicate measurements ($n=15$) on the ion abundance ratios for each phthalate was determined to calculate the precision of the calibration, and the relative standard deviations of the qualifier to the quantifying ion. The relative standard deviations on the relative abundances did not exceed 10% for all the phthalates tested. Additionally, where phthalates have similar fragmentation patterns (DnOP and DEHP), identification was by retention time. Good linearity of response was achieved for all phthalates with coefficient of correlation (r^2)>0.990. In full scan electron impact (EI) mode the limits of detection (LOD) [15] were calculated as three times the background noise, with values of the order of 0.1 μg/ml for the single isomers, and the limits of quantitation (LOQ) [15] as ten times the LOD with values of the order of 1 μg/ml. The LOD for DINP and DIDP were based on the lowest discriminating response for each of the isomeric profiles, with values between 2.5 and 3.5 μg/ml.

All phthalates, with the exception of dimethyl phthalate, show an intense characteristic base peak at *m/z* 149. Other peaks (Figs. 4 and 5) may be explained by double hydrogen transfer (DHT) [16,17]. The transfer of a single hydrogen gives rise to even mass ions that are of low intensity and may not be observed in the mass spectra. In the fragmentation pattern of DEHP (Fig. 6), two hydrogen atoms are transferred from the parent ion to the *m/z* 279 fragment. This ion is two mass units heavier than the cleaved fragment would be if unmodified.

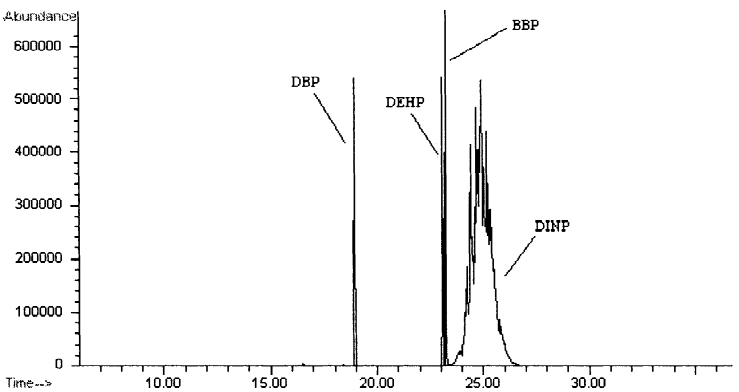


Fig. 3. Total ion chromatogram of dibutyl phthalate, bis(2-ethylhexyl) phthalate, benzyl butyl phthalate and diisononyl phthalate in full scan mode. Temperature programme and MS parameters are in GC–MS conditions.

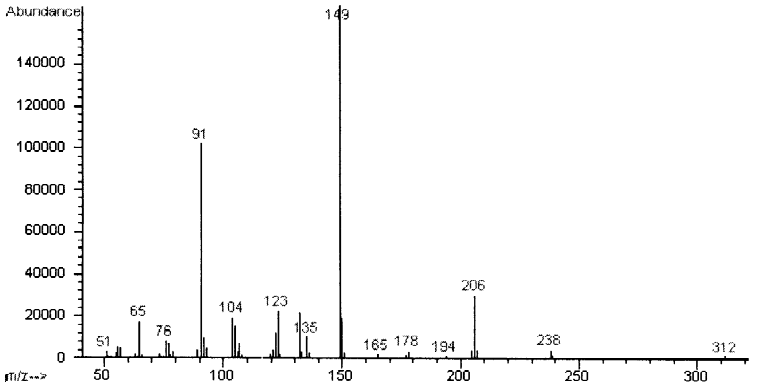


Fig. 4. Mass spectrum of benzyl butyl phthalate showing the base peak at m/z 149 and the qualifier ions at their relative intensities at m/z 91 and 206.

The molecular ion peak for phthalate compounds with long chain alkyl groups is usually weak and not always present in the mass spectra, but the $(M–R)^+$ and $(M–OR)^+$ (R = alkyl group) fragments can be a secondary form of identification. In the mass spectrum of BBP (Fig. 7) the presence of a highly abundant peak at m/z 91 is characteristic of the resonance stabilised benzyl cation ($C_6H_5 \cdot CH_2^+$).

Both migration methods were successfully validated through interlaboratory trial. The analytical data were subjected to statistical analysis [18,19]. The within laboratory repeatability and between laboratory reproducibility for the GC–MS and the agitation/extraction methods for the PVC reference disc were determined and are summarised in Tables 3–5. These results suggest that substantial variation is likely to arise from the agitation/extraction procedure. The repeatability for this method describes the precision expected from a set of replicate measurements made by a single laboratory with the same analyst, instrument and MS parameters, i.e. tuning. This gives an indication of the variation within method measurements. The standard deviation is used to calculate a repeatability limit ''*r*''. Reproducibility measurements are made by several laboratories, different analysts, instruments and tuning parameters. This gives the variation expected between sample measurements made in different laboratories. In this instance the reproducibility limit ''*R*'' is expressed.

The recoveries for the extraction methods, determined by six laboratories at the target spiking levels of 200 μg/ml for both DINP and DIDP, and 10 μg/ml for DEHP, ranged from 86 to 90% (Tables

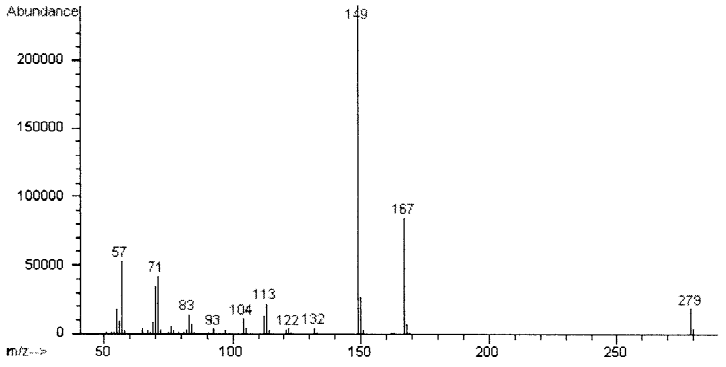


Fig. 5. Mass spectrum of bis(2-ethylhexyl) phthalate showing the base peak at m/z 149 and the qualifier ions at their intensities at m/z 279 and 167.

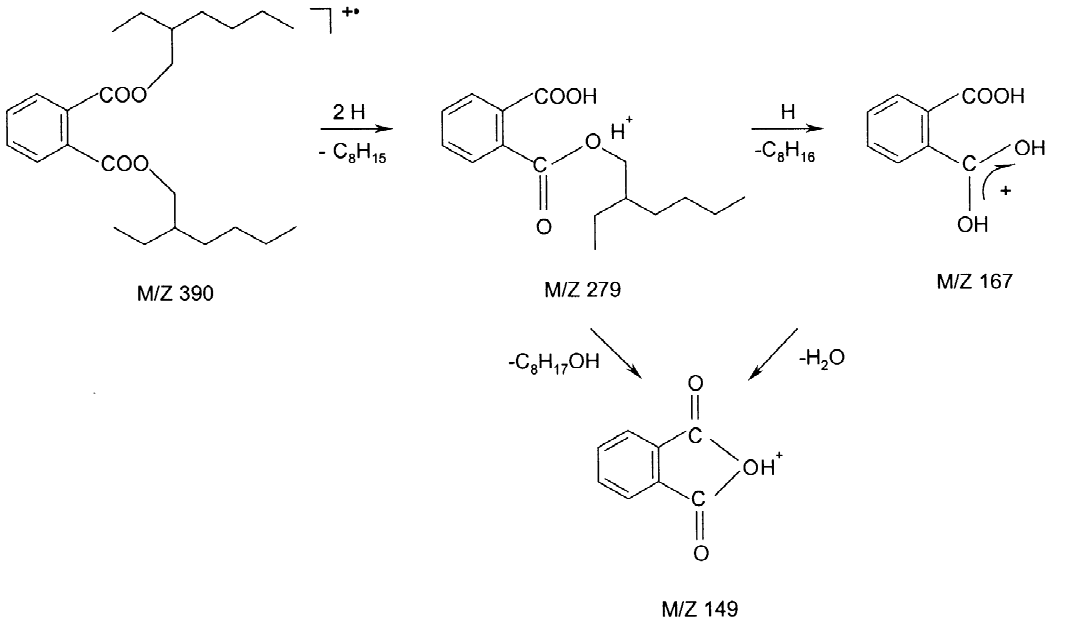


Fig. 6. General structure and characteristic fragmentation pattern of bis(2-ethylhexyl) phthalate.

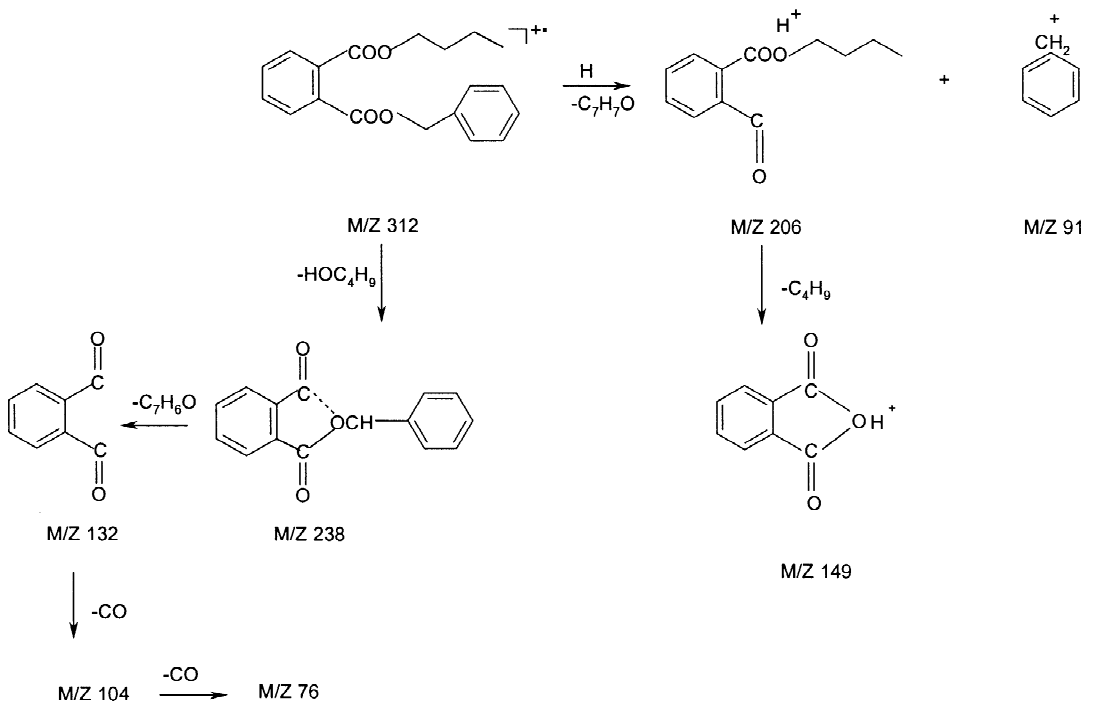


Fig. 7. General structure and characteristic fragmentation pattern of benzyl butyl phthalate.

Table 3
GC–MS repeatability (r) and reproducibility (R) determined from the results of all participating laboratories

Solution tested (μg/ml)	Mean (μg/ml)	C.V.% (r)[a]	C.V.% (R)[a]
DINP 250	253.9	9.8	8.1
DIDP 250	261.7	7.7	8.5
DEHP 10	11.0	11.4	11.9

Pure phthalate compounds were prepared in *n*-hexane and analysed by injecting onto GC–MS.

[a] C.V.% (r) = S_r/x where S_r is the repeatability standard deviation and x is the observed mean of the data. C.V.% (R) = S_R/x (S_R is reproducibility standard deviation).

4 and 5). Repeatability coefficients of variation (C.V.) ranged from 6.8 to 14.6%. Each analysis included a blank determination of the saliva simulant without the reference sample. Due to the background levels of phthalates in the method materials, trace amounts of DBP and DEHP were detected and blank subtracted from sample results

Each laboratory performed at least five replicate tests with the PVC reference disc. The mean migration values (1.43 μg/10 cm^2/min at 37 °C and 8.8 μg/10 cm^2/min at 65 °C) compared favourably with those from the DCG adult volunteer study, 1.4 μg/10 cm^2/min and 9.0 μg/10 cm^2/min, respectively.

Table 4
Migration test results—Simulated method—from the results of all participating laboratories

	Mean (%)	C.V.% (r)	C.V.% (R)
Solution tested			
DINP recovery (200 μg/ml)	90.0	8.4	
DIDP recovery (200 μg/ml)	87.1	14.6	
DEHP recovery (10 μg/ml)	86.4	6.8	
Repeatability and reproducibility of PVC disc			
DINP PVC reference disc	1.43[a]	21.9	35.3
Phthalate release from test samples			
DINP-fruit teether	0.7[a]	37.4	
DIDP-bath animal	1.2[a]	64.2	
DEHP-high chair	1.6[a]	39.4	
DEHP swimming armband	1.2[a]	5.5	

Recovery solutions were prepared in propan-2-ol, diluted in saliva simulant solution and extracted with dichloromethane. The extract was finally prepared in *n*-hexane for GC–MS analysis.

[a] μg/10 cm^2/min.

Table 5
Migration test results—Stringent method—from the results of all participating laboratories

	Mean (%)	C.V.% (r)	C.V.% (R)
Solution tested			
DINP recovery (200 μg/ml)	89.9	12.2	
DIDP recovery (200 μg/ml)	88.0	11.8	
DEHP recovery (10 μg/ml)	88.0	13.3	
Repeatability and reproducibility of PVC disc			
DINP PVC reference disc	8.8[a]	22.7	31.1
Phthalate release from test samples			
DINP-fruit teether	5.0[a]	23.3	
DIDP-bath animal	3.9[a]	33.1	
DEHP-high chair	4.1[a]	25.21	
DEHP swimming armband	3.1[a]	48.5	

See Table 4 for experimental detail.

[a] μg/10 cm^2/min.

The reproducibility C.V. (R) for all laboratories was similar for the two methods and is summarised in Tables 4 and 5. The differences in migration test results for commercial samples may be attributable to the morphology of individual test specimens, e.g. flexible, thin sheet materials and thick materials with exposed cut edges, and any variation in the preparation of the test samples. Preparation was a standardised procedure, but was performed individually by each participating laboratory. Although it would be preferable to test the toy and childcare articles in whole form, this is not practical, as the outer surface is the only area available to a child during mouthing. As a result, a 10 cm^2 sample area (total surface area including cut edge if the thickness of the test article is ≥1 mm) was prepared by punching with a ''metal punch''. The close agreement of the results with the Dutch human volunteer studies has been demonstrated. The Stringent method is most suitable for the assessment of toy and childcare articles intended to be mouthed, given that it meets the CSTEE target migration value of 9 μg/10 cm^2/min for DINP from the PVC reference material.

This study represents participating laboratories' first attempts at both the Simulated and Stringent methods. There are therefore strong grounds for anticipating that reproducibility would be improved on their repeated use of the methods.

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